REMARKS

Claims 25-41 and 44-55 are pending. Claims 50-52 and 55 are amended. The amendment is supported within the claims and throughout the specification. Claim 56 has been added. The claim is supported, for example, on page 7, line 5 of the application as filed. No new matter is presented. After entry of the amendment, claims 25-41 and 44-56 will be pending.

Claim Rejections

For the sake of brevity, the rejections under 35 USC §103(a) are summarized below and addressed in combination.

Claims 25-26, 29-30, 35-41 and 44-55 stand rejected under 35 U.S.C. §103(a) over Malvolti (WO 03/004005) in view of Hughes et al. (*The Lancet*, Vol. 361, No. 9375, pages 2114-2117, 2003).

Claims 25-26, 29-30, 36-41 and 44-55 stand rejected under 35 U.S.C. §103(a) over Montgomery (U.S. 6,083,922) in view of Hughes et al.

Claims 27-28 and 31-33 stand rejected under 35 U.S.C. §103(a) over Malvolti et al. in view of Hughes et al., as applied to claims 25-26, 29-30, 35-41 and 44-55, and further in view of Wiedmann et al. (U.S. 5,747,001).

Claim 34 stands rejected under 35 U.S.C. §103(a) over Malvolti et al. in view of Hughes et al., as applied to claims 25-26, 29-30, 35-41 and 44-55, and further in view of Azria et al. (U.S. 5,759,565).

Each of the rejections is traversed. The cited documents, even in the stated combinations, fail to teach or suggest the features of the present invention in any manner sufficient to sustain any one of the rejections.

The Office Action alleges that Malvoti and Montgomery disclose the claimed invention, except for the addition of a magnesium or calcium salt. Hughes is added to each of Malvoti and Montgomery for its teaching relative to the effect of isotonic magnesium administered adjunct to nebulized salbutamol. Hughes indicates that in the study on which the reference was based, the magnesium led to an enhanced bronchodilator response in severe asthma (in comparison to use of an isotonic saline solution).

The Examiner takes the position that one skilled in the art would have combined these elements, thus arriving at the present invention in an obvious manner.

The Examiner expressly acknowledges the deficiencies of Malvoti and Montgomery, but considers that the use of magnesium and calcium salts for inhalation solutions was logical in view of Hughes et al.

As for the remaining rejections, Wiedmann is added and applied for its disclosure of formulations with a surface modifier for nebulization. Likewise, Azria is added and relied on for its disclosure of viscosity and tonicity requirements.

Hughes et al. is applied in each of the 35 U.S.C. §103(a) rejections for its teaching relative to the effect of isotonic magnesium administered adjunct to nebulized salbutamol. Applicant submits, however, that Hughes et al. would not have suitably been combined with the other applied references as proposed. Even if it were, the combinations are still deficient and cannot sustain the rejections.

The Office Action lists the Graham factors that must be considered when making a rejection for obviousness. The MPEP in section 2141.01 discusses considerations in determining the scope and content of the prior art and ascertaining the differences between the prior art and the claims at issue, including determining if the art is analogous art. Specifically, the MPEP states:

> The examiner must determine what is "analogous prior art" for the purpose of analyzing the obviousness of the subject matter at issue. **>"Under the correct analysis, any need or problem known in the field of endeavor at the time of the invention and addressed by the patent [or application at issue] can provide a reason for combining the elements in the manner claimed. " *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1397 (2007). Thus a reference in a field different from that of applicant's endeavor may be reasonably pertinent if it is one which, because of the matter with which it deals, ***logically would have commended itself to an inventor's attention in considering his or her invention as a whole.***

Applicant submits that neither the cited references nor the instantly claimed invention are being considered as a whole. When considered as a whole, the references cannot be properly combined, and moreover, the references cannot be properly applied to the instant claims as Hughes logically would have not commended itself to an inventor's attention in considering his or her invention as a whole.

The Hughes reference cited by the Examiner in each of the rejections is directed to compositions and methods for the treatment of ***severe asthma using magnesium sulphate*** as demonstrated by the title. The instantly claimed invention provides an antibiotic agent (i.e., not an agent for the treatment of asthma) and methods for treating a subject with a respiratory infection (i.e., not a subject with asthma).

As noted by the Examiner, Hughes does teach that "Use of isotonic magnesium as an ***adjuvant to nebulized salbutamol*** results in an enhanced bronchodilator response in the treatment of severe asthma" (last sentence of abstract). The instant claims are not drawn to an agent or method for the treatment of asthma.

Hughes teaches that magnesium sulphate is an adjuvant to salbutamol, suggesting that magnesium sulphate acts with salbutamol, providing complementary therapeutic benefits. As the action of salbutamol and tobramycin are distinct with distinct activities for the treatment of distinct conditions, it would not be expected that a compound that was complementary to one would be complementary to the other.

Applicant notes that Hughes teaches that prior to the study discussed in the reference, the effectiveness of isotonic magnesium sulphate as an adjuvant to nebulized salbutamol in severe asthma attacks was unknown (see abstract).

Hughes provides a mechanism of action for magnesium in the treatment of asthma. Specifically, Hughes states:

> Hypomagnesaemia has been implicated in chronic asthma through mechanisms involving modulation of inflammatory processes.[1,2] Magnesium is also a powerful relaxant of smooth muscles in the airway,[3,4] and this is the mechanism through which intravenous magnesium is proposed to have a substantial bronchiodilator effect in treatment of severe exacerbations of asthma in children and adults.[5-12] (first full paragraph of introduction)

There is no teaching or suggestion that respiratory infection includes hypomagnesaemia or smooth muscle constriction. Therefore, there can be no motivation based on the teachings of Hughes to administer magnesium for the treatment of infection. Hughes cannot be considered to be an analogous art to the pending claims, or to be analogous art to the other references cited by the Examiner related to the administration of an antibiotic agent. Moreover, as discussed below, the references combined with Hughes teach the advantage of formulations having lower salt concentrations. Therefore, there can be no motivation to modify the teachings of the references to provide formulations with higher salt concentrations.

Further, Hughes teaches that even within the context of asthma, "previous attempts to administer magnesium by nebulization have shown mixed results" (second paragraph of introduction). Hughes notes "some, but not all studies have shown that magnesium administered before challenge testing can cause a dose-dependent reduction in bronchial hyper-responsiveness." Hughes discusses eight studies with conflicting results as to the effect of magnesium in the treatment of asthma depending on the subjects, the severity of the asthma, the cause of the asthma, etc. ***Provided with eight studies, Hughes could not predict the results of his study. Any***

assertion that the results based on the modification of other references in view of Hughes cannot stand. Moreover, although the study of Hughes provides statistically significant data on the usefulness of isotonic magnesium for the treatment of severe asthma in adults at a single dosage level for a highly select group, Hughes provides no further certainty for the use of nebulized magnesium at other doses or in other groups of asthmatics, never mind those with respiratory bacterial infections.

Provided with this uncertainty in the condition studied, asthma, there can be no teaching or suggestion regarding the effects of magnesium in the treatment of infection which does not include either hypomagnesaemia or bronchial constriction, the conditions to be treated by administration of magnesium. Therefore, in considering the scope of the prior art and the differences between the prior art and the claims at issue, the present claims cannot be obvious in view of the cited art.

The Graham factors further include resolving the level of ordinary skill in the art. Although the level of ordinary skill in the art for the development of formulations for and methods of medical treatment is high, those of ordinary skill understand that results from one study on the effects of nebulized magnesium in the treatment of asthma cannot predict the outcome of another study on the effect of nebulized magnesium in the treatment of asthma, as demonstrated by the eight conflicting studies discussed by Hughes. Further, one of skill in the art of treating respiratory infections would not look to a compound to treat hypomagnesaemia or bronchial constriction (e.g., magnesium) as these symptoms are not features of respiratory bacterial infection.

A prior art reference must be considered in its entirety, i.e., ***as a whole, including portions that would lead away from the claimed invention***. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984) Although the Hughes reference does teach that nebulized magnesium sulphate is useful ***as an adjuvant to salbutamol in the treatment of severe asthma in adults***, the reference teaches a careful selection of subjects for the

study, therefore, the results of the study would provide information only for treatment of the specific group for study selected. Moreover, the existence of the study itself demonstrates that the prior asthma studies could not predict the results that would be obtained in the adult severe asthma study. The reference as a whole demonstrates that asthma cannot be considered a single homogeneous condition. Extrapolation of the results from the asthma study performed by Hughes to the treatment of a respiratory infection cannot be properly done. This would be understood by one of skill in the art. ***One of skill in the art would not expect that the inclusion of magnesium sulphate in an antibiotic agent would provide any benefit in the treatment of a bacterial infection.*** The mere fact that various components from each of the references can be combined is not sufficient motivation to combine the references. Hughes teaches the inclusion of magnesium in therapeutic compositions for the treatment of conditions not associated with pulmonary bacterial infection. There can be no motivation based on Hughes to include magnesium in a composition for the treatment of pulmonary bacterial infection.

Provided with the differences between asthma and infection, one of skill in the art would not be motivated to add magnesium sulphate to a formulation including tobramycin for administration by nebulization. First, one would not expect to derive any benefit from the administration of magnesium sulphate to a subject with a respiratory infection as the etiology of asthma and infection are distinct. Second, applicant notes that a review of the literature after the filing date of the instant application teaches that there is still no demonstrable advantage to administering magnesium sulphate by nebulizer to a subject with asthma. In their meta-analysis, Mohammed and Goodacre (2007, Intravenous and nebulized magnesium sulphate for acute asthma: systematic review and meta-analysis. *Emerg. Med. J.* 24:823-830, copy enclosed) demonstrates that even after the filing date of the instant application, the utility of administration of nebulized magnesium sulphate for the treatment of asthma was equivocal at best. Specifically, the abstract states:

> Nebulized treatment was associated in adults with weak evidence of an effect upon respiratory function (SMD 0.17, 95% CI –0.02 to 0.36; p = 0.09), and hospital admission (RR 0.68, 95% CI 0.46 to 1.02; p = 0.06), and in children with no significant effect upon respiratory function (SMD -0.26, 95% CI -1.49 to 0.98; p = 0.69) or hospital admission (RR 2.0, 95% CI 0.19 to 20.93; p = 0.56).

Therefore, even if the effects of an adjuvant in an asthma study could be predictive of the effects of the same adjuvant in a respiratory infection study, which they cannot, the Mohammed and Goodacre review teaches that nebulized magnesium has no significant effect in asthma. Hughes demonstrates that with selection of the appropriate study, one can identify a study that has the desired results. However, when looked at as a whole, the data demonstrate that one of skill in the art would not expect to be successful in treating asthma with nebulized magnesium. Further, one cannot expect to be successful treating respiratory infection with nebulized magnesium.

> A rationale to support a conclusion that a claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods ***with no change in their respective functions***, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1395 (2007); *Sakraida v. AG Pro, Inc.*, 425 U.S. 273, 282, 189 USPQ 449, 453 (1976); *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57, 62-63, 163 USPQ 673, 675 (1969); *Great Atlantic & P. Tea Co. v. Supermarket Equipment Corp.*, 340 U.S. 147, 152, 87 USPQ 303, 306 (1950). (MPEP 2143.02)

As noted above, per the teachings of Hughes, ***the function of magnesium in the treatment of asthma is the treatment of hypomagnesaemia and bronchial constriction***. As these symptoms are not a part of bacterial infection, the function of magnesium in a formulation for the treatment of pulmonary infection must necessarily change. Similarly, the activity of salbutamol and tobramycin cannot be seen as compounds having the same function. Therefore, substitution of one compound for the other cannot be considered obvious.

Further, Applicant submits that Malvolti cannot be modified to include additional salt. The Office Action states that Malvolti teaches the aerosolization of an "isotonic solution... containing tobramycin sulfate in 4 ml of half-saline aqueous solution.... [and that a] **quarter normal saline**... formulation **is more** efficiently nebulized... compared to a tobramycin formulated in 0.9% normal saline" (page 3, emphasis in original). Therefore, as emphasized in the Office Action, Malvolti teaches the advantage of the use of a solution having lower salt. Therefore, Malvolti cannot be modified with the teachings of the Hughes reference to include additional salt. If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984) Malvolti cannot be modified to include additional salt. Therefore, Malvolti cannot be properly be modified to include the teachings of Hughes.

Similarly, the Office Action notes the statements of Montgomery regarding the advantages of formulations having lower salt concentrations and that "Higher amounts of tobramycin was delivered when tobramycin was formulated in ¼ **diluted saline** than tobramycin formulated in *full strength normal saline*" (see page 6 of the Office Action, emphasis in original). Therefore, Montgomery teaches the advantages of the use of lower salt formulations. Montgomery cannot be modified to include additional salt. Therefore, Montgomery cannot be properly be modified to include the teachings of Hughes.

The Wiedmann and Azria references cannot compensate for the failings of the Hughes, Malvolti, and Montgomery references.

As the references cannot be properly combined they cannot make obvious the instantly claimed invention. Withdrawal of the rejections is respectfully requested.

In view of the above amendments and remarks, Applicant believes the pending application is in condition for immediate allowance.

FEE AUTHORIZATION

The Commissioner is authorized to charge the fee for a Request for Continued Examination to Deposit Account, No. 04-1105, Reference 65177(45107). It is believed that no further fees are due with the instant response. However, if an additional fee is due, the Commissioner is authorized to charge any fees associated with this submission or any other submission from our Office in relation to this application the Deposit Account noted above referencing the Docket Number. Any overpayment should be credited to said Deposit Account.

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